In the Claims:

The accompanying paper requests cancellation of all pending claims except claim 40, without prejudice or disclaimer.

Please amend claim 40 as follows:

40. (Amended) A method for [identifying] binding a transforming growth factor β (TGF-β) protein in a sample, comprising contacting said sample with [an] a purified mammalian LTBP-2 or LTBP-3 protein or polypeptide under conditions effective to allow binding [and detecting the protein so bound] of said LTBP-2 or LTBP-3 protein or polypeptide to said TGF-β protein; wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

Please add new claims 43-78, as follows:

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43. The method of claim 40, wherein said sample is located within an animal and said LTBP-2 or LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind TGF-β in said animal.

44. A method of binding TGF-β, comprising contacting a composition comprising TGF-β with a composition comprising a purified mammalian LTBP-2 or LTBP-3 protein or polypeptide in an amount effective to bind TGF-β; wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

45. The method of claim 44, wherein said composition comprising TGF-β is located within an animal and said composition comprising said LTBP-2 or LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind TGF-β in said animal.

46. A method of using an LTBP-2 or LTBP-3 protein, polypeptide or peptide, comprising providing to an animal a biologically effective amount of a purified mammalian LTBP-2 or LTBP-3 protein, polypeptide or peptide that comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

47. The method of claim 46, wherein an amount of an LTBP-2 or LTBP-3 protein, polypeptide or peptide effective to generate anti-LTBP-2 or anti-LTBP-3 antibodies is provided to said animal.

48. The method of claim 47, wherein an LTBP-2 or LTBP-3 peptide of between 15 and about 50 amino acids in length is provided to said animal.

49. The method of claim 47, wherein an LTBP-2 or LTBP-3 peptide of between 15 and about 30 amino acids in length is provided to said animal.

50. The method of claim 47, wherein antisera comprising said anti-LTBP-2 or anti-LTBP-3 antibodies is collected from said animal.

51. The method of claim 46, wherein an amount of an LTBP-2 or LTBP-3 protein or polypeptide effective to bind TGF-β is provided to said animal.

52. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β regulates TGF-β activity in said animal.

53. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β modulates the activation of TGF-β in said animal.

54. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β modulates the activation of latent complexes that comprise TGF-β, thereby regulating TGF-β activity.

55. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β targets TGF-β to the extracellular matrix in said animal.

56. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β targets TGF-β to the bone matrix in said animal.

57. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β targets TGF-β to connective tissues in said animal.

58. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β targets TGF-β to the cell surface of cells in said animal.

59. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β protects TGF-β from proteolytic attack and activation in said animal.

60. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β protects TGF-β from proteolytic attack and activation during wound repair or tissue healing in said animal.

61. The method of claim 51, wherein said LTBP-2 or LTBP-3 protein or polypeptide is a recombinant protein or polypeptide prepared by expressing an LTBP-2-encoding or LTBP-3-encoding DNA segment in a recombinant host cell and purifying the expressed LTBP-2 or LTBP-3 protein or polypeptide away from total recombinant host cell components.

62. The method of claim 51, wherein said TGF-β is located within a tissue healing, wound repair tissue site or bone progenitor tissue site of said animal and wherein said LTBP-2 or LTBP-3 protein or polypeptide is provided to said tissue site.

63. The method of claim 62, wherein said TGF-β is located within a tissue healing or wound repair tissue site of said animal.

64. The method of claim 62, wherein said TGF-β is located within a bone progenitor tissue site of said animal.

65. The method of claim 62, wherein said LTBP-2 or LTBP-3 protein or polypeptide is provided to said tissue site by contacting said tissue site with a composition comprising a nucleic acid segment that expresses said LTBP-2 or LTBP-3 protein or polypeptide in cells of said tissue site.

66. The method of claim 65, wherein said LTBP-2 or LTBP-3 protein or polypeptide is provided to said tissue site by contacting said tissue site with a composition comprising said nucleic acid segment and a structural biocompatible matrix.

67. The method of claim 65, wherein said nucleic acid segment is a DNA segment.

68. The method of claim 65, wherein said nucleic acid segment is an RNA segment.

69. The method of claim 51, wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least about thirty contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

70. The method of claim 51, wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least about fifty contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

71. The method of claim 51, wherein said LTBP-2 or LTBP-3 protein or polypeptide exhibits at least 90% identity to the amino acid sequence set forth in SEQ ID NO:2 or SEQ ID NO:4, respectively.

72. The method of claim 51, wherein said LTBP-2 or LTBP-3 protein or polypeptide exhibits between 91% and about 99% identity to the amino acid sequence set forth in SEQ ID NO:2 or SEQ ID NO:4, respectively.

73. The method of claim 51, wherein an LTBP-2 protein comprising the amino acid sequence of SEQ ID NO:2 is provided to said animal.

74. The method of claim 51, wherein an LTBP-3 protein comprising the amino acid sequence of SEQ ID NO:4 is provided to said animal.

75. A method of using an LTBP-2 or LTBP-3 protein or polypeptide, comprising administering to an animal a purified mammalian LTBP-2 or LTBP-3 protein or polypeptide in an amount effective to bind TGF-β in said animal; wherein said LTBP-2 or LTBP-3 protein or polypeptide specifically binds TGF-β and comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

76. A method of binding TGF-β within a repair or bone progenitor tissue site of an animal, comprising contacting said tissue site with a purified mammalian LTBP-2 or LTBP-3 protein or polypeptide, or a nucleic acid that expresses said LTBP-2 or LTBP-3 protein or polypeptide, to

provide an amount of said LTBP-2 or LTBP-3 protein or polypeptide effective to bind TGF-β in said animal; wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

77. A method of binding TGF-β, comprising administering to an animal a composition comprising a purified mammalian LTBP-2 or LTBP-3 protein or polypeptide in an amount effective to bind TGF-β in said animal; wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

78. A method of binding TGF-β, comprising administering to an animal a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind TGF-β in said animal; wherein said LTBP-3 protein or polypeptide binds TGF-β and comprises at least fifteen contiguous amino acids present in SEQ ID NO:4 or exhibits at least 90% identity to the amino acid sequence set forth in SEQ ID NO:4. --.

REMARKS

I. Status of the Claims

The accompanying paper requests cancellation of all pending claims except claim 40, without prejudice or disclaimer. Presently, claim 40 is being amended to even further improve its clarity. New claims 43-78 have been added, which are supported by the original specification and parent applications incorporated therein by reference (see below). Numbering the present

claims starting with claim 43 is believed to be correct as the copy of the specification enclosed concludes with claim 42.

Claims 40 and 43-783 are therefore in the case. For the convenience of the Examiner, a copy of the pending claims is attached hereto as **Exhibit A**.

II. Continuing Application Status

The present application is a continuing application based upon allowed application Serial No. 08/479,722 ("the '722 application; Attorney Docket Nos. 4100.000500, UMIC:013). The inventorship remains the same as the earlier application.

A copy of the claims that will issue from the '722 application is enclosed as **Exhibit B**. The claims canceled from the '722 application in light of a restriction requirement are also provided herewith as **Exhibit C**.

III. Other Parent Applications

The parent, '722 application is a continuation-in-part of PCT Application PCT/US95/02251, filed February 21, 1995 (Attorney Docket Nos. 4100.000410, UMIC:009P); which is a continuation-in-part of U.S. Application Serial Number 08/316,650 ("the '650 application; Attorney Docket Nos. 4100.000300, UMIC:003), filed September 30, 1994; which is a continuation-in-part of U.S. Application Serial Number 08/199,780 ("the '780 application; Attorney Docket Nos. 4100.000200, UMIC:002), filed February 18, 1994. The '650 application matured into U.S. Patent No. 5,942,496, and the '780 application earlier matured into U.S. Patent No. 5,763,416.

The entire text and figures of each of the '650 and '780 applications were specifically incorporated by reference into the '722 application on filing (see '722 application at page 2, opening paragraph).

A copy of the claims to issue from the '650 application is enclosed as **Exhibit D**. The claims that issued from the '780 application are provided as **Exhibit E**, and the original claims in the '780 application are shown in **Exhibit F**.

IV. Amendments to the Specification

As the grandparent ('650) and great grandparent ('780) applications were specifically incorporated by reference into the immediate parent ('722) application (see page 2), the text of the '650 and '780 applications forms part of the present disclosure. An amendment is presently being introduced into the instant specification from those earlier applications, to which priority is still claimed. This addition is fully supported by the original '650 and '780 applications and, for convenience of review, may be correlated with the issued claims in those cases attached as **Exhibit D** and **Exhibit E**.

Incorporation of material into the specification by reference is proper. *Ex parte Schwarze*, 151 USPQ 426 (Bd. App. 1966). Incorporation by reference of one or more issued U.S. patents, at the time of filing the application, also provides the enabling support required by 35 U.S.C. § 112, first paragraph, for any claims advanced in the new application that rely on the same standard of teaching of "how to make and use" as the claims in the issued patent(s).

Other issued U.S. patents that concern the use of exogenous growth factors in methods for treating bone defects or inducing bone formation *in vivo* are also incorporated by reference into the '722 specification. For example, U.S. Patent No. 4,877,864, which concerns the

administration of a therapeutic composition of bone inductive protein to treat cartilage and/or bone defects, and U.S. Patent 5,108,753, which concerns the use of a device containing a pure osteogenic protein to induce endochondral bone formation and for use in periodontal, dental or craniofacial reconstructive procedures ('722 specification at pages 30 and 83).

Upon agreement concerning allowable subject matter, Applicants intend to amend the 'Summary of Invention' section to add the precise language of the allowed claims. In the interest of efficiency for both the Applicants and the Office, it seems most appropriate to defer amendment of the Summary until agreement on allowability.

Certain amendments to the specification are also being made to conform the specification to the formal drawings enclosed herewith. These amendments, each of which were entered during prosecution of the '722 application, are fully supported by the original text and drawings.

V. Support for the Claims

Support for the present claims is to be found throughout the original parent ('722) application and in the grandparent ('650) and great grandparent ('780) applications, each specifically incorporated into the '722 application by reference and now progressed to issue.

In addition to finding support throughout the present specification, the language of the current claims matches that found to be acceptable in the parent applications, including the definitions of the proteins, polypeptides, peptides and nucleic acids from the '722 application and the tissue site and gene-matrix embodiments from the '650 and '780 applications. For the convenience of the Examiner, copies of the allowed claims from each of the three parent applications are attached hereto as **Exhibits B, D** and **E**. Additional support for the present claims exists in the specification and parent applications as follows.

Claim 40 is based upon the original claim (**Exhibit C**), although "identifying" has been replaced with "binding". Claim 44 is also based upon a version of claim 40 that includes the "binding" terminology. "Binding TGFβ" is evidently an inherent property of latent TGFβ binding proteins (LTBPs) and is supported by the entire '722 specification (*e.g.*, see page 47, line 14 and page 68, line 5).

The LTBP-2 and LTBP-3 proteins and polypeptides in all independent claims are defined as "purified, mammalian" proteins or polypeptides, as in the claims allowed in the parent application (**Exhibit B**).

In independent claims 40, 44, 46, 75, 76 and 77, the language comprising "at least fifteen contiguous amino acids present in SEQ ID NO:4", as allowed in the parent application in reference to LTBP-3 (**Exhibit B**), has also been adapted for LTBP-2. In independent claim 78, which refers to LTBP-3 alone, the protein or polypeptide is defined in the alternative as either comprising at least fifteen contiguous amino acids from SEQ ID NO:4 or exhibiting at least 90% identity to the amino acid sequence of SEQ ID NO:4. These definitions were allowed in claims 127 and 145 of the '722 application (**Exhibit B**).

Dependent claims 43 and 45 qualify independent claims 40 and 44 by reciting that the LTBP-2 or LTBP-3 proteins or polypeptides are administered to an animal to bind TGF-β. These claims are supported throughout the '722 application, *e.g.*, at least at page 29, line 10 through page 30, line 28; page 44, line 30 through page 48, line 8; page 57, line 17 through page 58, line 29; and at page 71, line 7 through page 74, line 2.

Similarly, independent claim 46 recites methods of use in which LTBP-2 or LTBP-3 proteins, polypeptides or peptides are administered to an animal, and is supported by the '722 application at least at page 2, lines 12-14; page 29, line 10 through page 30, line 28, as

exemplified by page 29, line 11 and page 30, lines 22-28; page 41, line 19 through page 42, line 4; page 44, line 30 through page 48, line 8; page 57, line 17 through page 58, line 29; page 71, line 7 through page 74, line 2; and at page 127, line 4.

Claims 47 and 50 concern the administration of LTBP-2 or LTBP-3 proteins, polypeptides or peptides to generate anti-LTBP-2 or anti-LTBP-3 antibodies and antisera that may be collected from an animal. These are supported by Section 8 of the Detailed Description and in Example II of the '722 application, see, *e.g.*, page 40, lines 25-27. The exemplary peptides of between 15 and about 50 or 30 amino acids in length, as defined in claims 48 and 49, are supported by allowed claims 130 and 131 in the '722 application (**Exhibit B**).

Dependent claims 51 through 60 recite various functional outcomes of LTBP binding to TGF-β, and are supported throughout the '722 application, notably by Sections 9 and 10 of the Detailed Description and in Example I. Basically, as TGF-β has the ability to regulate tissue remodeling and wound repair (see pages 2-8, 46, 47 and 57), and as LTBPs bind TGF-β (Example I), LTBPs are useful in the regulation of tissue remodeling and wound repair.

The production and storage of TGF-β as a latent complex that is activated only under certain physiological (or pathological) conditions provides for the precise regulation of TGF-β (pages 4, 6, 8, 47, 57, 71 and 73). LTBPs both regulate and target TGF-β activity (pages 45 and 71) and help ensure TGF-β integrity *in vivo* (page 46). By protecting TGF-β from proteolytic attack under pathological conditions, LTBPs will moderate aberrant effects, such as reducing scar tissue during wound healing. LTBPs thus contribute to TGF-β regulation through a sophisticated feedback loop (pages 71 and 73).

For particular written description support for claims 52 through 60, see page 45, line 23 (claim 52; regulates TGF-β activity); page 46, line 5 and page 58, lines 22-27 (claims 53 and 54;

modulates the activation of latent complexes that comprise TGF-β); page 46, line 1 and page 58, lines 19-22 (claim 55; targets TGF-β to the extracellular matrix); page 48, lines 4-5 (claim 56; targets TGF-β to the bone matrix); page 45, line 29 and page 58, line 18 (claim 57; targets TGF-β to connective tissues); page 46, line 2 and page 58, lines 27-29 (claim 58; targets TGF-β to the cell surface); and page 3, lines 14, 15, 26 and 27; page 4, line 14; page 6, line 29; page 28, line 9; page 46, lines 7-11 and page 58, lines 27-29 (claims 59 and 60; protects TGF-β from proteolytic attack and activation, as in wound repair and tissue healing).

Claim 61 defines the LTBP-2 or LTBP-3 proteins or polypeptides as recombinant proteins or polypeptides and is based upon original claim 22 (**Exhibit C**).

Each of claims 62-64 define the location of the TGF-β within the animal as a tissue healing, wound repair tissue site or bone progenitor tissue site. These are again supported throughout the '722 application, notably by Sections 1-4, 9 and 10 of the Detailed Description and Example I (see also pages 2-8, 22, 27, 28, 46, 47, 57 and 58, particularly page 3, lines 26-27; page 4, line 14; page 6, line 29; page 28, line 9; page 46, lines 8-11; page 47, lines 19-22; and page 48, line 1). The "repair" and "bone progenitor" tissue sites also correlate with the language of the gene-matrix method claims allowed in the grandparent ('650) and great grandparent ('780) applications (**Exhibit D** and **Exhibit E**).

Claims 65-68 concern the use of nucleic acids (claim 65) and nucleic acid-structural matrix compositions (claim 66) to provide the LTBP-2 or LTBP-3 protein or polypeptide to TGF-β in a repair or bone progenitor tissue site of an animal. Both DNA (claim 67) and RNA (claim 68) nucleic acids may be employed (see also claims 161 and 162 of the '722 application, **Exhibit B**). RNA may be preferred in certain embodiments, particularly as traversal of the nuclear envelope is not necessary for expression.

The use of nucleic acids and nucleic acids in functional association with structural matrices are predominantly supported by the '650 and '780 applications specifically incorporated by reference into the '722 application (see **Exhibits D, E** and **F**). Accordingly, such language is being introduced into the present application by amendment at a convenient point of the detailed description. Incorporation of material into the specification by reference is proper. *Ex parte Schwarze, supra.*

Exemplary LTBP-2 and LTBP-3 proteins and polypeptides for use in the claimed invention are described in claims 69 through 74. These claims are based upon those allowed in the '722 application (see claims 128, 129, 138 and 144-146 of **Exhibit B**).

Claims 75 through 78 are variations of earlier claims presented in independent form. Support for these claims is as described above, *e.g.*, for claim 75, see claims 46, 43, 45 and 51; for claim 76, see claims 51, 43, 45 and 62-64; for claim 77, see claim 51; and for claim 78, which refers to LTBP-3 only, see claims 51 and 71.

It will therefore be understood that no new matter is included within the present claims.

VI. Formalities

Applicants' representative, Shelley Fussey, has changed law firms since the parent application was filed. A new Power of Attorney was submitted in the parent application and an additional copy is enclosed herewith. All communications should be directed to the address listed therein and at the end of this document.

Formal drawings are included herewith.

No fees should be due in addition to the enclosed filing fees. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Assistant

Commissioner is authorized to deduct said fees from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4100.000582.

VII. Conclusion

The present claims are believed to be condition for allowance, and an early indication to this effect is respectfully requested. Should Examiner Fitzgerald have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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